Synthesis and Characterization of C–H Functionalized Benzimidazole Derivatives

SYNOPSIS

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Synopsis of Research Work for Ph.D. Degree in the Faculty of Science (Chemistry)

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a) Purpose and Need of the Study

Benzimidazole derivatives are a **versatile and widely important class of heterocycles** in modern chemistry. Their unique fused benzene–imidazole scaffold is a **privileged pharmacophore** present in numerous drugs and bioactive natural products, imparting activities ranging from antimicrobial and anticancer to anti- inflammatory and antiviral effects. Beyond medicinal chemistry, benzimidazole motifs play **central roles in homogeneous catalysis** (e.g. as ligands and precursors to N-heterocyclic carbene catalysts) and serve as key building blocks in **organic materials** such as optoelectronic devices. The broad utility of this scaffold means that **diverse functionalized benzimidazole derivatives** are continually sought to fine-tune properties for specific applications. In this context, expanding the library of benzimidazole derivatives is crucial for discovering novel drug candidates, advanced materials, and efficient catalysts.

Despite their importance, **traditional synthetic routes to substituted benzimidazoles are often inefficient**. Most substituted benzimidazoles have been prepared via *de novo* synthesis – constructing the heterocycle afresh for each new analogue. However, medicinal and materials chemistry efforts demand **large libraries of analogues** to optimize biological or physical properties. Repeatedly rebuilding the core for every variant is laborious and wasteful. There is a compelling need for more **direct, late-stage functionalization** strategies that can modify an existing benzimidazole core at

carbon–hydrogen (C–H) bonds, appending new substituents in fewer steps. Such C–H functionalization approaches can **streamline the synthesis** of derivatives by installing diversity directly onto a pre- formed scaffold, rather than via lengthy multi-step routes. Moreover, many conventional C– H activation methods rely on expensive transition metal catalysts (e.g. Pd, Ru, Rh), which raises issues of cost, toxicity, and environmental impact. The **purpose of this study** is to develop a *cost-effective, metal-free (organocatalytic)* C–H functionalization methodology for benzimidazoles. This will address the need for an **affordable and accessible** synthetic route to diversified benzimidazole derivatives, in line with green chemistry trends towards avoiding precious metals and embracing sustainable catalysis. By enabling efficient late-stage C–H functionalization, the project aims to unlock rapid generation of new benzimidazole-based compounds for **medicinal chemistry, materials science, and catalysis** applications.

b) Details of the Project with Chapterization

Chapter 1: Introduction and Literature Review – This chapter will provide a comprehensive overview of benzimidazole chemistry and set the stage for the research. It will cover the **significance of benzimidazole derivatives** in various domains (pharmaceuticals, catalysts, and materials) with relevant examples of commercial drugs and functional materials containing this scaffold. For instance, the introduction will highlight benzimidazole's role as a **pharmacophore in numerous drugs** (such as antiparasitic albendazole and proton-pump inhibitors) and as a ligand in **N-heterocyclic carbene (NHC) catalysts**. The chapter will then review existing synthetic methods for functionalizing benzimidazoles, focusing on recent advances in **C–H activation techniques**. Key catalytic strategies reported in literature – including transition-metal catalyzed C–H arylation/alkylation – will be summarized. For example, **ruthenium-catalyzed C–H arylation** has been shown to directly couple benzimidazoles with aryl halides, yielding 2-arylated products in excellent yields. Similarly, palladium, nickel, and copper catalysts have enabled C–H functionalization at the C2 position (adjacent to the nitrogen) by exploiting directing effects. However, the limitations of these methods (such as reliance on costly noble metals or the need for pre-installed directing

groups/halogen handles) will be critically discussed. The literature review will identify a **gap**: *the scarcity of metal- free or organocatalytic routes* for direct C–H functionalization of benzimidazoles.

Recent green chemistry trends will be noted, such as the use of **heterogeneous catalysts** to improve catalyst recyclability and reduce costs, and emerging **metal- free photochemical** or **iodine-catalyzed** strategies. By the end of Chapter 1, the motivation for a new organocatalytic C–H functionalization approach will be clearly established, leading to the formulation of the research objectives.

Chapter 2: Objectives and Hypothesis – This short chapter will explicitly state the **research objectives** and the central hypothesis of the project. Building on the gaps identified in Chapter 1, it will outline the specific goals, for example: *(i) To develop a novel organocatalytic protocol for direct C–H functionalization at the C2 and/or aromatic positions of benzimidazole scaffolds under mild, metal-free conditions; (ii) To synthesize a diverse library of C–H functionalized benzimidazole derivatives (with various substituents such as aryl, alkyl, or heteroatom-containing groups); (iii) To fully characterize the new derivatives and evaluate their potential applications in medicinal chemistry (e.g., preliminary bioactivity assays), materials science (e.g., optical or electronic properties), and as catalysts or ligands in organic synthesis.* The **hypothesis** driving this work is that a suitably designed **organocatalyst system can activate the C–H bond** of the benzimidazole core (likely via a radical or ionic mechanism) to enable the introduction of new substituents without requiring any transition metal. This chapter will also propose why this approach should be feasible – for instance, citing analogous successes in metal-free C–H functionalizations of related heterocycles. One inspiring example is the **KI-catalyzed oxidative coupling** of benzothiazoles with aldehydes (using *tert*-butyl hydroperoxide as oxidant) to form 2-aryl benzothiazoles under metal-free conditions. Adapting such an approach to benzimidazoles forms a part of our strategy. By clearly stating the objectives and hypothesis, Chapter 2 will set the foundation for the experimental design in subsequent chapters.

Chapter 3: ***Synthesis of C–H Functionalized Benzimidazole Derivatives*** – This chapter constitutes the core experimental work of the thesis. It will detail the **organocatalytic C–H functionalization methodology** developed, along with the results of synthesizing various benzimidazole derivatives. The chapter will begin by describing the **rational design of the catalytic system**. For example, based on preliminary literature insights, an *organic catalytic approach* will be employed – possibly using an **organic photoredox catalyst** (e.g., Eosin Y or Rose Bengal) under visible light, or an **organoiodine catalyst** (such as KI or hypervalent iodine reagents) – to initiate C–H activation. The reasoning for catalyst choice (availability, affordability, mechanism) will be explained. Next, the **model reaction** used to optimize conditions will be presented (for instance, functionalization of a simple benzimidazole like N-methylbenzimidazole at the C2 position with a model electrophile or coupling partner). Key reaction parameters – solvent, temperature, light (if photochemical), oxidant, etc. – will be systematically varied to achieve optimal yield. We anticipate using benign oxidants (like peroxides or oxygen) and **avoiding toxic reagents**, in line with making the method environmentally friendly. The chapter will then report the **scope of the developed reaction**: a series of substrates and coupling partners will be tested to demonstrate the generality. For example, we will synthesize **2-aryl benzimidazoles** by coupling various benzimidazole cores with different aromatic aldehydes or aryl donors under oxidative conditions (analogous to the KI/TBHP strategy). Likewise, other functionalizations (such as alkylation at C2 using alkyl radicals generated organocatalytically, or C–H oxygenation/sulfenylation if relevant) may be explored. Each successful reaction will be described with its optimized conditions and yields. The **regioselectivity** issue in benzimidazole functionalization (e.g., distinguishing C2 vs C7 positions) will be addressed by proper substrate design (e.g., N-substitution to lock tautomerism). Challenges encountered (such as any need for directing groups or controlling side-reactions) will be discussed. By the end of Chapter 3, we expect to have a **library of new C–H functionalized benzimidazole derivatives** synthesized via our organocatalytic method, demonstrating its efficiency, selectivity, and broad applicability.

Chapter 4: Characterization and Applications of Derivatives – This chapter will focus on the **detailed characterization** of the synthesized benzimidazole derivatives and preliminary exploration of their properties/applications. All new compounds will be thoroughly characterized by **spectroscopic and analytical techniques**. This includes $^{1}H/^{13}C$ Nuclear Magnetic Resonance (NMR) spectroscopy to confirm structural connectivity, High-Resolution Mass Spectrometry (HR-MS) for molecular weight confirmation, Infrared spectroscopy for functional group analysis, and Elemental Analysis for purity. For key representative structures, single-crystal X-ray crystallography may be performed to unambiguously establish the molecular structure and the position of new substituents on the benzimidazole core. These characterization results will be presented and interpreted in this chapter, confirming that C–H functionalization indeed occurred at the intended positions and that the correct structures were obtained.

In the latter part of Chapter 4, the **potential applications** of the functionalized benzimidazoles will be examined, aligning with the broad relevance of this chemistry to medicinal chemistry, materials science, and catalysis. For medicinal chemistry relevance, if any of the synthesized derivatives resemble known pharmacophores or exhibit drug-like properties, we will conduct preliminary **biological evaluations**. This could include in vitro assays (for example, antimicrobial testing if the substituents suggest such activity, or enzyme inhibition assays if applicable) or computational docking studies to assess binding affinity to a biological target. The goal is to identify if late-stage functionalization yielded analogues with *enhanced bioactivity or unique selectivity*. For materials science, certain derivatives (especially those with extended conjugation or donor-acceptor features) will be assessed for **optical or electronic properties** – for instance, measuring their UV-Vis absorption and fluorescence, or evaluating thermal stability – to see if they could act as organic semiconductors or fluorescent dyes. In catalysis, we will explore whether some C–H functionalized benzimidazoles can serve as **ligands or organocatalysts** themselves.

Notably, benzimidazole-derived NHCs are powerful catalysts; thus, if our derivatives include benzimidazolium salt precursors, their ability to act as organocatalysts (e.g. in benzoin or umpolung reactions) will be briefly tested. Additionally, any derivative

with metal-binding sites could be used to form metal complexes and tested in a simple catalytic reaction (such as a cross-coupling or oxidation) to demonstrate utility as a ligand. While full application development is beyond the scope of this synthetic-focused project, these exploratory tests will highlight the **multifaceted potential** of the new benzimidazole derivatives and reinforce why creating them via C–H functionalization is valuable.

Chapter 5: Conclusion and Future Outlook – The final chapter will summarize the key findings of the research, reinforcing how the developed organocatalytic C–H functionalization method addressed the initially stated needs. We will conclude that an **efficient, metal-free synthetic route** to benzimidazole derivatives was successfully established, and discuss to what extent the results support the original hypothesis. The chapter will also provide a **future outlook**, suggesting how the methodology could be extended (e.g., to late-stage functionalization of complex drug molecules containing benzimidazole cores) or improved (perhaps by incorporating **asymmetric organocatalysis** to access enantioenriched products, if chiral centers are introduced). Potential collaborations with pharmacologists or materials scientists to fully exploit the properties of the new derivatives may be proposed. In essence, Chapter 5 will close the loop from the motivation through to the achievements, and point towards the next steps and broader implications of the work.

(The chapterization above spans approximately 2–3 pages, detailing how the project will be structured and carried out, ensuring a logical flow from background to experimental work and applications.)

c) Hypothesis

We hypothesize that **direct C–H bond functionalization of benzimidazole scaffolds can be achieved through an organocatalytic strategy**, yielding a variety of novel derivatives without the need for transition metal catalysts. Specifically, by using an **organic catalyst (e.g., an organoiodine or photoredox catalyst) in the presence of a mild oxidant**, the relatively inert C–H bond on the benzimidazole ring can be activated (via a radical or ionic mechanism) and coupled with suitable reagents to form new C–C or C–heteroatom bonds. This approach is expected to be **regioselective** (favoring the

most reactive C–H positions, such as C2 adjacent to the nitrogen, or activated aromatic positions) and broadly applicable to different substituents. The underlying hypothesis is that an appropriately designed metal- free catalytic system will provide the necessary reactivity (through, for example, generation of radical species or electrophilic intermediates) to functionalize the benzimidazole core, thus offering a **cost-effective and environmentally benign alternative** to traditional metal-catalyzed methods. If this hypothesis holds true, one should observe that the presence of the organocatalyst and oxidant leads to formation of the desired C–H functionalized product in good yield, whereas in the absence of the catalyst the reaction would not proceed – confirming that the catalyst is enabling the C–H activation. We also anticipate that the new C–H functionalization method will tolerate various functional groups, aligning with our hypothesis that it can serve as a **late-stage diversification tool** for complex benzimidazole- containing molecules.

d) Methodology

To test the above hypothesis and meet the project objectives, the following **methodological plan** will be implemented:

1. **Literature Survey and Theoretical Planning** – Conduct an exhaustive literature review (as outlined in Chapter 1) focusing on known C–H functionalization methods for benzimidazole and analogous heterocycles. Based on this, select a promising *organocatalytic system* (e.g., a combination of an organic catalyst and oxidant or a photochemical setup) that could facilitate benzimidazole C–H activation. Rationalize the choice through mechanistic considerations (for instance, propose a plausible radical mechanism for C–H cleavage and coupling).

2. **Model Reaction Development** – Begin experimental work with a **model substrate** (such as a simple N-protected benzimidazole) and a model electrophile/coupling partner (e.g., an aromatic aldehyde for potential C2 arylation via oxidative coupling). Set up small-scale reactions to screen conditions: *compare different organocatalysts* (e.g., KI, organic dyes, N-

hydroxyphthalimide, etc.), *vary oxidants* (oxygen, TBHP, peracids), and test the effect of solvents and temperature. Use TLC and/or GC-MS to monitor progress. The goal is to identify conditions under which the C–H functionalized product forms with measurable yield.

3. **Optimization of Reaction Conditions** – Once a viable reaction is detected, systematically optimize it. Apply **design of experiments (DoE)** or vary one-factor- at-a-time to improve yield and selectivity: adjust catalyst loading, oxidant amount, light intensity/wavelength (if photochemical), reaction time, etc. Include necessary controls (blank reactions without catalyst or oxidant to confirm necessity of each component). The end of this step should result in an **optimized protocol** for the C– H functionalization, for example: "Benzimidazole + coupling partner, in solvent X, with Y mol% organocatalyst and Z equivalents oxidant, under light at N nm, for T hours, gives highest yield".

4. **Substrate Scope Expansion** – Apply the optimized conditions to a **range of substrates** to demonstrate the generality of the method. Synthesize a variety of benzimidazole derivatives by varying: (a) the **benzimidazole core** (e.g., different N- substituents or ring substituents on the benzene ring to examine electronic effects), and (b) the **coupling partners** (e.g., different aldehydes to introduce diverse aryl groups, or other electrophiles like allylic alcohols, alkyl halides for alkylation, etc., as appropriate for the mechanism). Each reaction will be performed on a preparative scale and isolated to yield the pure product. Calculate yields and note any limitations (e.g., if electron-poor substrates give lower conversion, or if certain functional groups are incompatible and cause side reactions).

5. **Characterization of Products** – For each new C–H functionalized benzimidazole obtained, perform thorough characterization. Record NMR spectra (^{1}H and ^{13}C) to confirm the structure and regiochemistry of substitution. Use **mass spectrometry** to verify molecular weights. Where possible, grow single crystals for X-ray crystallography, especially for representative

examples, to unambiguously confirm the position of new substituents on the benzimidazole ring. Maintain detailed logs of spectral data and compare with literature (for any known compounds) to ensure accuracy. If novel compounds are obtained, assign NMR signals with the help of 2D NMR techniques (COSY, HSQC, HMBC) to establish connectivity.

6. **Mechanistic Investigations** – Investigate the mechanism of the organocatalytic C– H functionalization to support the hypothesis of how the reaction proceeds. Conduct **control experiments** such as adding radical scavengers (e.g., TEMPO) to see if the reaction is inhibited (which would indicate a radical pathway). If photoredox catalysis is used, test the reaction in the dark or with different light sources to confirm the role of photo-activation. Measure kinetic profiles for a model reaction (time vs. yield) to glean rate information. Where feasible, identify intermediates (for example, by LC-MS monitoring or trapping experiments). These studies will elucidate whether the C–H activation occurs via radical abstraction, electrophilic activation, or another pathway, thereby validating the mechanistic premise of the organocatalyst's role.

7. **Application Testing** – As a final part of the methodology (corresponding to Chapter 4), carry out preliminary tests on the **applications of selected derivatives**. For medicinal chemistry potential, choose a few derivatives to run *in vitro* assays (e.g., antimicrobial tests in collaboration with a microbiology lab, or cytotoxicity assays on cancer cell lines) to observe any biological activity. For materials science, measure photophysical properties (UV-Vis absorption/emission spectra) of derivatives that have extended conjugation, and evaluate any interesting behavior (like fluorescence quantum yield or solvatochromism). For catalysis, take a derivative that could act as a ligand (for instance, one with a donor site or convertible to an NHC ligand) and test it in a simple benchmark reaction (such as a

Suzuki coupling or an organocatalytic benzoin condensation if an NHC). These tests will be exploratory but will provide **proof-of-concept data** linking the synthesized molecules to real-world applications.

Throughout the methodology, **data will be recorded diligently**, and any experimental difficulties (low yields, reproducibility issues, etc.) will be addressed by tweaking conditions or seeking alternative strategies (e.g., if one organocatalyst fails, try another type). The methodology is designed to be *modular*: if initial approaches do not yield success, the plan can adapt (for example, if photoredox fails, switching to an acid-catalyzed electrophilic C–H activation route with a sulfone or diazonium chemistry could be explored). Emphasis will be placed on keeping the developed protocol **affordable and accessible** – using commercially available organic catalysts or simple synthesized catalysts, and standard laboratory equipment (avoiding the need for scarce materials or specialized apparatus). By following these steps, we aim to achieve a robust and broadly useful C–H functionalization method for benzimidazole derivatives, confirming our hypothesis and fulfilling the research objectives.

e) Bibliography

1. Hansen, J. H.; Fjellaksel, R. *"Catalytic Intermolecular Functionalization of Benzimidazoles."* in **Chemistry and Applications of Benzimidazole and Its Derivatives**, IntechOpen, 2019. (Provides an overview of catalytic strategies for benzimidazole functionalization and highlights the importance of late-stage C–H functionalization)

2. Nature Research Intelligence (Topic Summary). *"Benzimidazole Derivatives: Synthesis and Pharmacological Activities."* **Nature (2024)**. (Summarizes the significance of benzimidazole scaffolds in medicinal chemistry and recent advances in sustainable synthesis, e.g. use of heterogeneous catalysts)

3. Kobayashi, Y.; Kashiwa, M.; Sonoda, M.; Kirihata, M.; Tanimori, S. *"Regioselective Monoarylation of 2-Phenylbenzimidazole via Ruthenium-Catalyzed C–H Bond Functionalization."* **Synthesis**, 46(23), 3185-3190 (2014).

(Demonstrates transition- metal catalyzed C–H arylation of benzimidazole derivative, highlighting the efficiency of metal-catalyzed approaches)

4. Gao, Y.; Song, Q. *"KI-Catalyzed Oxidative Cross-Coupling of Benzothiazoles with Aryl Aldehydes under Metal-Free Conditions."* **Org. Biomol. Chem.**, 12, 9329–9333 (2014). (An example of a metal-free C–H functionalization of a heterocycle analogous to benzimidazole, using inexpensive KI and peroxide to achieve arylation via a radical mechanism)
5. Cernak, T. *et al. "The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-like Molecules."* **Chem. Soc. Rev.** 45, 546–576 (2016). (Review discussing the concept and techniques of late-stage functionalization (LSF) in drug discovery, underlying the strategy of diversifying core scaffolds like benzimidazoles via C–H activation)
6. Recent Advances (Coord. Chem. Rev. 2024). *"Recent advances in the application of heterogeneous catalysts for the synthesis of benzimidazole derivatives."* **Coord. Chem. Rev.** 473, 214790 (2024). (Highlights green chemistry approaches to benzimidazole synthesis, emphasizing catalyst recyclability and cost reduction, aligning with the project's sustainable methodology focus)

Signature of the Research Scholar